Amendments to the claims are fully supported by the specification and the claims as originally filed.

No new matter has been added.

In amending or canceling claims, Applicants reserve the right to pursue claims of equivalent or different scope in this and later applications. No claim amendment or cancellation should be viewed as an acquiescence to a rejection.

REJECTION OF CLAIMS 1-14, 37-42 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

"New Matter"

The Examiner argues that "The sequence of IL-1B allele 2 (+6912) was initially disclosed as one in which the nucleotide at position 6912 was a G residue. The specification was subsequently amended to redefine this allele as comprising a C residue at position 6912." The Examiner continues, "Because there appears to be no support in the specification as filed for a C residue at position 6912 of Fig. 1, Fig. 2, SEQ ID NO:1, or SEQ ID NO:2, nor at position 8845 of SEQ ID NO:1 or SEQ ID NO:2, the claims as amended recite new matter."

The Examiner further notes:

> In order to overcome this rejection, Applicants must establish that, at the time of filing, they were in possession of the claimed invention, *i.e.* a polynucleotide identical to that disclosed in Figure 1, except that it comprises a C rather that a G at position 6912. Furthermore Applicants must establish that the IL-1B sequence comprising a G residue at position 6912 (human IL-1B GEN XO4500) was recognized in the prior art as the wild type sequence, and that the nucleic acid of the instant invention is, in fact, not the wild type.

Applicants were in possession of an IL-1B allele having a C rather than a G at the position corresponding to +6912 in Figures 1 and 2. As described in the instant application (Example 1, pp.36-37), a PCR product corresponding the 3' UTR of the IL-1B gene was amplified from human genomic DNA and sequenced. As noted in the attached Declaration from Dr. Francesco di Giovine, the sequencing revealed a novel G to C mutation that is referred to as IL-1B (+6912) allele 2. This sequencing data is provided and clearly shows that the isolated

nucleic acid has a C at the appropriate position. As stated by Dr. Duff, this data was obtained prior to the filing date of February 10, 1999.

Applicants respectfully suggest that whether or not the sequence defined as Genbank XO4500 is art-recognized as "the wild-type sequence" is irrelevant to the case at hand. Applicants contend that the IL-1B sequence with the IL-1B (+6912) allele 2 (G to C mutation) is not presented in the prior art. Nonetheless, Applicants note that data presented in the instant application (Example 2, pp. 37-38) demonstrate that the G to C mutation (allele 2) is the rarer allele, while allele 1, corresponding to Genbank sequence XO4500, is the more common allele.

Accordingly, Applicants request permission to enter an amended Sequence Listing and an amended Figure 2. The amended Figure 2 is submitted herewith, along with a copy of the original Figure 2 showing the change in red ink and a Letter to the Draftsperson.

Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112.

"Written Description"

The Examiner argues:

> Claim 42 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey...that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Solely to expedite prosecution and not in acquiescence to the rejection, claim 42 is cancelled, thereby obviating the rejection.

"Enablement"

The Examiner argues, "The disclosure fails to enable the claimed invention because it does not provide convincing biochemical evidence which links the overexpression of IL-1B to any disease, and because no such evidence is present in the prior art."

Applicants respectfully maintain that the specification does provide evidence that overexpression of IL-1B is linked to many diseases. Nonetheless, to expedite prosecution and not in acquiescence to the rejection, claims 1 and 6 have been amended to remove reference to causation by an inappropriately high level of IL-1β.

Applicants note that one of skill in the art can practice the claimed invention regardless of whether or not the IL-1B (+6912) allele 2 causes overexpression of IL-1B in any disease. As described in the accompanying Declaration of Dr. Francesco di Giovine, an allele may be associated with a disorder, and therefore be of prognostic value, whether or not that allele causes the disorder in question. An allele may be considered associated with a disorder if it is linked (or in "linkage disequilibrium" with) an allele that is itself known to be associated with a disorder (for a discussion of these issues, see WO 98/54359, cited by the Examiner, pp.1 - 2). For example, IL-1B (+3954) allele 2 is associated with periodontal disease, psoriasis, insulin-dependent diabetes and many other disorders (eg. see WO 98/54359, Duff et al., cited by Examiner). Therefore, the detection of IL-1B (+3954) allele 2 in a subject indicates that the subject is predisposed to each of those disorders. The instant application teaches (see for example, pp. 44-46 and Table 3) that subjects carrying the IL-1B (+3954) allele 2 are greater than 99% likely to carry IL-1B (+6912) allele 2. Therefore detecting the IL-1B (+6912) genotype will be at least as predictive as detecting the IL-1B (+3954) allele 2.

For these reasons, Applicants submit that in order to be enabling, the specification need only teach that IL-1B (+6912) allele 2 is in linkage disequilibrium with alleles that are themselves associated with one or more disorders. The specification does teach this (eg. see Example 6), and therefore Applicants respectfully conclude that the Application meets the requirements for enablement under 35 U.S.C. § 112, first paragraph.

The Examiner has maintained his rejection of claims 37 - 39 and 42 under 35 U.S.C. 112, first paragraph. Applicants disagree with the Examiner for reasons already made of record. In order to expedite prosecution, and not in acquiescence to the rejection, claims 37-39 and 42 are canceled, obviating the rejection.

In view of these arguments and amendments, Applicants request the reconsideration and withdrawal of these rejections under 35 U.S.C. § 112, first paragraph.

REJECTION OF CLAIMS 35 AND 36 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner states:

> Applicant should consider redrafting the claim such that it is drawn to an isolated nucleic acid comprised of between 100 and 7000 bases of SEQ ID NO:2, but which comprises a cytosine rather than a guanine at a position corresponding to position 8845 of SEQ ID NO:2.

While Applicants disagree with the reasons for rejection, to expedite prosecution, claim 35 has been amended to conform with the Examiner's recommended claim language.

REJECTIONS UNDER 35 U.S.C. §102 AND § 103

The Examiner has variously rejected claims under 35 U.S.C. §102(b) and §103 in view of Clark et al. (Nuc. Acids Res. 14(20): 7897-7914, 1986) and Clark et al. (GenBank Acc. No. X04500).

The Examiner further states:

> Claim 34 as amended are still drawn to SEQ ID NO:2, which is the exact sequence disclosed by Clark. The sequence of SEQ ID NO:2 cannot be changed by amendment. Changes to the Sequence Listing may only be made by submission of a new Sequence Listing, and such changes must be fully supported in the Application as filed. In this case, Applicant will be allowed to file a new Sequence Listing with a corrected version of SEQ ID NO:2 only if the new matter rejection outlined above can be overcome.

Applicants request permission to submit a new Sequence Listing providing the appropriate sequence for the IL-1B (+6912) allele 2, as discussed in the accompanying Declaration of Dr. Francesco di Giovine. Applicants note that upon filing a revised sequence listing, the claims will relate to sequences that are distinct from those of either Clark et al. reference. Applicants maintain that neither Clark reference anticipates or renders obvious a nucleic acid comprising the IL-1B (+6912) allele 2. Furthermore, no secondary reference provided by the Examiner cures the defects of the Clark et al. references.

Accordingly, Applicants request reconsideration and withdrawal of these rejections under 35 U.S.C. 102(b) and 103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims, both those originally filed and those newly added, are now in condition for allowance and early notification to this effect is earnestly solicited. If the Examiner believes that an interview would expedite the prosecution of this application, the Applicants would ask that the Examiner please contact their representative identified below at the Examiner's convenience.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FOLEY, HOAG& ELIOT

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John D. Quisel
Reg. No. P-47,874
Agent for Applicants

Patent Group
Foley, Hoag & Eliot, LLP
One Post Office Square
Boston, MA 02109-2170
Tel.: (617) 832-1000
Fax: (617) 832-7000